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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002950469 for a patent by COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION as filed on 30 July 2002.

WITNESS my hand this
Fifth day of August 2003

J. Billingsley

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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: **Improved biomedical compositions**

The invention is described in the following statement:

IMPROVED BIOMEDICAL COMPOSITIONS

Technical Field of the Invention

This invention relates to ethylenically unsaturated macromonomers that are suitable for use as precursors for polymers that have biomedical applications, and in particular as injectable precursors for intraocular lenses (IOLs).

Background of the Invention

As adults age the accommodative power of the eye decreases leading to the onset of presbyopia. This age-related decrease in accommodative power is believed to be caused by a decrease in the elasticity of the lens material. This decrease is probably caused by cross-linking of the lens material. Thus the loss of accommodation results from a change in elasticity rather than a decrease in the action of the ciliary muscles. The replacement of the original lens with a synthetic polymer having the elasticity equivalent to the lens of a young adult offers the prospect of being able to use a surgical procedure to replace the need for glasses to correct presbyopia.

The use of polymeric prostheses and biomedical mouldings has grown rapidly in recent times. Such mouldings may be used for contact lenses or for specific ophthalmic purposes. For example, they may be used for intraocular lenses and eye bandages. They may also be used for surgical mouldings such as heart valves and artificial arteries. Other applications include wound dressings, biomedical adhesives and tissue scaffolds. Use in drug delivery is a further application.

Diseases of the lens material of the eye are often in the form of cataracts. The ideal cataract procedure is considered to be one where the lens capsule bag is maintained with the cataractous lens material removed through a small opening in the capsule. The residual lens epithelial cells are removed chemically and/or with ultrasound or lasers. A biocompatible artificial lens material (IOL) with appropriate optical clarity, refractive index and mechanical properties is inserted into the capsular bag to restore the qualities of the original crystalline lens. The desired refractive index is about 1.41. For many years most of the IOLs were made of poly(methylmethacrylate) (PMMA), a material with good optical characteristics and compatibility with tissues in the eye. However, PMMA is a very rigid material

and the incision must be made big enough, at least 5-6 mm, for implantation of the lens. With improved devices for removal of the natural lens that require only small (3-4 mm) incision, there was a need for lenses which are foldable.

There have also been recent advances in methods of inserting intraocular lens. For example, US Patent number 5,772,667 assigned to Pharmacia Lovision Inc, discloses a novel intraocular lens injector. This device compresses an intraocular lens by rolling the lens into a tight spiral. The device then injects the compressed lens through a relatively small incision in the eye, approximately 2- 3 millimetres in length, resulting from a phacoemulsification procedure. The intraocular lens is inserted into a receiving channel of the injector device in an uncompressed state and is urged into a cylindrical passageway. As the intraocular lens advances into the cylindrical passageway, the lens rolls upon itself into a tightly rolled spiral within the confines of the cylindrical passageway. An insertion rod is then inserted into an open end of the cylindrical passageway and advances the compressed lens down the passageway. As the lens exits the passageway and enters the eye, the lens will expand back to its uncompressed state. Although those implanted lenses offered significant advances the implantation of these types of lenses still require the patient to use spectacle correction for reading.

To avoid the need for such injection devices and to also overcome the limitation of conventional IOL of requiring reading spectacles, it has been proposed that intraocular lenses be formed *in situ* after being injected as a liquid flowable form into the lens capsule bag. However, while this concept is attractive in that smaller incisions would be required, it raises further difficulties in that further chemical reactions are required to cure the injectable material and these are required to be not harmful to the patient. It is also a requirement that the chemical reactions can take place over a relatively short time under mild reaction conditions. It is desirable that the reaction is also not significantly inhibited by oxygen. A still further requirement is that no by-products or residues are produced that may have an adverse biological effect on the patient.

In our co-pending international patent application PCT/AU00/00915 prior art relating to ethylenically unsaturated macromonomers is discussed and an invention

relating to novel macromonomers suitable for use as injectable precursors for IOLs are described.

Although the macromonomers described in that specification meet many of the requirements for the preferred end use application we have now found a new class of macromonomer that provides IOLs with superior properties.

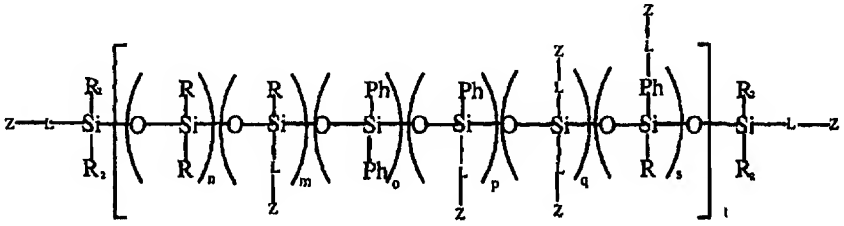
Summary of the Invention

This invention provides in one form an ethylenically unsaturated macromonomer comprising a polysiloxane copolymer having a backbone structure derived from siloxane monomer units that are substituted or unsubstituted arylsiloxanes, arylalkysiloxanes, alky(alkyl)siloxanes of the general formula $-R_1R_2SiO-$ and wherein the terminal groups of the copolymer backbone include ethylenically unsaturated groups and wherein pendent from the backbone are at least two ethylenically unsaturated groups.

Preferably the ethylenically unsaturated groups are (meth)acryl groups.

Preferably the (meth)acryl groups are (meth)acrylamide groups.

In an alternative form the present invention provides:



(I)

wherein

R = C_1 to C_6 alkyl, or perfluoronated C_1 to C6 alkyl;

R_2 = C_1 to C_6 alkyl, CF_3 or L-Z groups;

L = spacer group

Z = an ethylenically unsaturated free radical polymerisable group

t = 1 to 30

n = 50 to 100

m = 0 to 5

o = 0 to 50

p = 0 to 2

q = 0 to 2

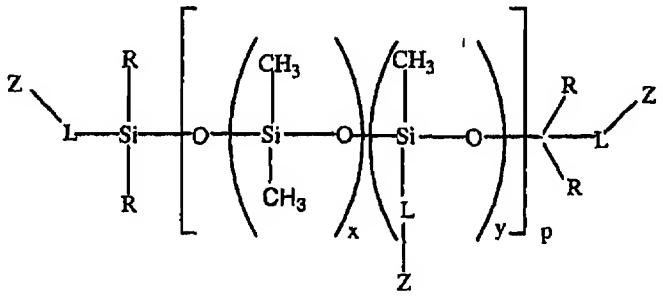
s = 0 to 2

The macromonomers set out in the above scheme of reaction as well as in Formula I are preferably random copolymers. However block type copolymers and alternating copolymers also fall within the scope of the present invention.

The spacer or linker group, L, functions as a group which allows the required ethylenic unsaturated group Z to be attached to the copolymer backbone. It may be a linear, branched or cyclic hydrocarbon chain. It may contain hetero atoms as well as carbonyl and other substituted atoms.

The term (meth)acryl group includes acryl or substituted acryl, such as methacryl, moieties attached through a variety of linkages including ester, amide and urethane linkages, or functional analogues of (meth)acryl capable of undergoing crosslinking reactions with a photoinitiator. Examples of functional acryl groups include acrylamidopropyl, methacrylamidopropyl, acryloxyhexyl and methacryloxyhexyl.

In a preferred form the invention provides



(II)

wherein R, L and Z are defined above and x = 90 to 100, y = 1 to 10, and p = 3 to 15.

In a still further form the invention provides a method of preparing a macromonomer of Formula I or Formula II wherein hydride terminated groups, preferably tetramethyldisiloxane, are used as intermediate reactants with cyclic oligomers.

Detailed Description of the Invention

The macromonomers of the present invention offer the advantage that they contain more crosslinkable or reactable groups per polymer chain than some of the prior art polymers but exhibit the desired mechanical and optical properties, particularly when used as an injectable precursor for an IOL.

This is an advantage because statistically the more crosslinkable groups per chain, the greater the probability of each individual polymer chain being incorporated into the polymer network. Accordingly, extractables after cure are anticipated to lower as a result of these additional crosslinkable groups. Locating the ethylenically unsaturated groups at each end of the chain is advantageous as it allows low extractables while retaining good viscoelastic properties in the cured or crosslinked polymer.

The macromonomers set out in the above scheme of reaction as well as in Formula I are preferably random copolymers. However block type copolymers also fall within the scope of the present invention.

The macromonomers of this invention may be polymerised by free radical polymerisation to form crosslinked or cured polymers. The mechanical and optical properties of the polymers are preferably matched to those of the natural biological material. In the case of lens material for the eye the refractive index should be close to 1.41. The modulus (E) of the polymer is measured by a Micro Fourier Rheometer in the range 0.01 – 100 kPa, preferably 0.1 – 10 kPa and most preferably 0.5 – 5kPa. The E modulus is influenced by the number of ethylenically unsaturated groups per macromonomer and also the spacing of the ethylenically unsaturated groups. Generally as the number of ethylenically unsaturated groups per macromonomer molecule increases or the spacing between ethylenically unsaturated groups decreases the elasticity of the cured polymer decreases.

The crosslinking process is preferably carried out in such a way that the resulting network polymer is free or essentially free from undesired constituents. A particular undesired constituent is starting macromonomers that have had none of their polymerisable groups incorporated into the network and as such are potentially extractable from the resulting network polymer after cure. The macromonomer is

preferably used without the addition of a comonomer although this is allowed. While generally the compositions of the present invention do not usually involve the use of other macromonomers, these may be optionally included. This can be an advantage when the refractive index or viscosity needs to be adjusted. Preferably the compositions comprise at least 50%, more preferably at least 80%, by weight of macromonomers as defined in the present invention.

In the case of photo cross-linking, it is expedient to add an initiator which is capable of initiating free-radical crosslinking. It is preferred that the initiators are activated by light in the visible spectrum rather than UV light as this enables the use of super visible light. Examples thereof are known to the person skilled in the art; suitable photoinitiators which may be mentioned specifically are benzoins, such as benzoin, benzoin ethers, such as benzoin methyl ether, benzoin ethyl ether, benzoin isopropyl ether and benzoin phenyl ether, and benzoin acetate; acetophenones, such as acetophenone, 2,2-dimethoxyacetophenone and 1,1-dichloroacetophenone; benzil, benzil ketals, such as benzil dimethyl ketal and benzil diethyl ketal, camphorquinone, anthraquinones, such as 2-methylanthraquinone, 2-ethylanthraquinone, 2-tert-butylanthraquinone, 1-chloroanthraquinone and 2-amylanthraquinone; furthermore triphenylphosphine, benzoylphosphine oxides, for example 2,4,6-trimethylbenzoyl-diphenylphosphine oxide; Eosin homologues such as Eosin Y, Phloxine, Rose Bengal and Erythrosin; benzophenones, such as benzophenone and 4,4'-bis(N,N'-dimethylamino)benzophenone; thioxanthones and xanthenes; acridine derivatives; phenazine derivatives; quinoxaline derivatives and 1-phenyl-1,2-propanedione 2-O-benzoyl oxime; 1-aminophenyl ketones and 1-hydroxyphenyl ketones, such as 1-hydroxycyclohexylphenyl ketone, phenyl 1-hydroxyisopropyl ketone, 4-isopropylphenyl 1-hydroxyisopropyl 1-hydroxyisopropyl ketone, 2-hydroxy-1-[4-2(-hydroxyethoxy)phenyl]-2-methylpropan-1-one,1-phenyl-2-hydroxy-2-methylpropan-1-one, and 2,2-dimethoxy-1,2-diphenylethanone, all of which are known compounds.

Particularly suitable photoinitiators, which are usually used with visible light sources are IRGACURE®819, Eosin homologues such as Rose Bengal, Eosin B, and fluorones such as H-Nu 470, H-Nu635 and derivatives.

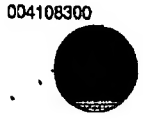
Particularly suitable photoinitiators, which are usually used with UV lamps as light sources, are acetophenones, such as 2,2-dialkoxybenzophenones and hydroxyphenyl ketones, in particular the initiators known under the trade names IRGACURE®651 and IRGACURE®184. A particularly preferred photoinitiator is IRGACURE®819.

The photoinitiators are added in effective amounts, expediently in amounts from about 0.05 to about 2.0% by weight, in particular from 0.1 to 0.5% by weight, based on the total amount of cross-linkable macromonomer. In addition the photoinitiator can be incorporated /grafted onto the polymer backbone. Such immobilisation of the polymer has the advantage of reducing the availability of photoinitiator residues for extraction post cure.

The resultant cross-linkable macromonomer can be introduced into a mould using methods known per se, such as, in particular, conventional metering, for example dropwise. Alternatively, the macromonomers may be cured *in situ*, as for example in the case of an injectable lens. In this case the macromonomer is cured or crosslinked in the lens capsule after injection.

The cross-linkable macromonomers which are suitable in accordance with the invention can be crosslinked by irradiation with ionising or actinic radiation, for example electron beams, X-rays, UV or VIS light, ie electromagnetic radiation or particle radiation having a wavelength in the range from about 280 to 750 nm. Also suitable are UV lamps, He/Dc, argon ion or nitrogen or metal vapour or NdYAG laser beams with multiplied frequency. It is known to the person skilled in the art that each selected light source requires selection and, if necessary, sensitisation of the suitable photoinitiator. It has been recognised that in most cases the depth of penetration of the radiation into the cross-linkable macromonomer and the rate of curing are in direct correlation with the absorption coefficient and concentration of the photoinitiator.

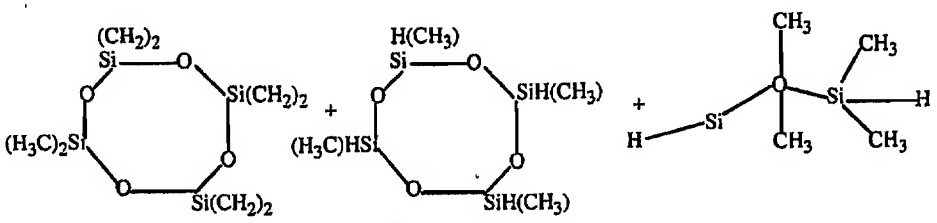
If desired, the crosslinking can also be initiated thermally. It should be emphasised that the crosslinking can take place in a very short time in accordance with the invention, for example, in less than twelve hours, preferably in less than hour, more preferably in less than 30 minutes. It will be appreciated that while the

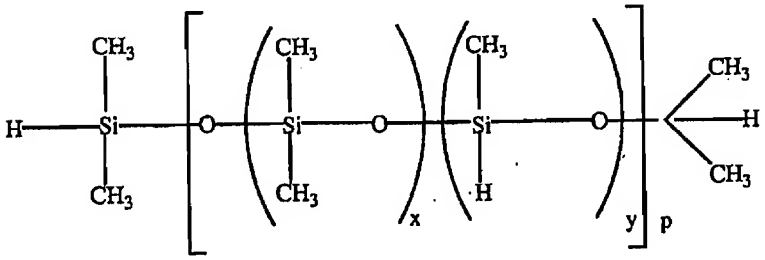


macromonomers of this invention may be used alone to form the lenses and other biocompatible materials, other materials may also be present. For example, diluents may be present as well as other monomers including other macromonomers. When used as an injectable material the macromonomers should have a viscosity in the range 1,000 – 150,000 cSt and more preferably 1,000 – 60,000 cSt at 25°C. Instruments such as the Brookfield rheometer or the Bohlin controlled stress rheometer may be conveniently used for measurement.

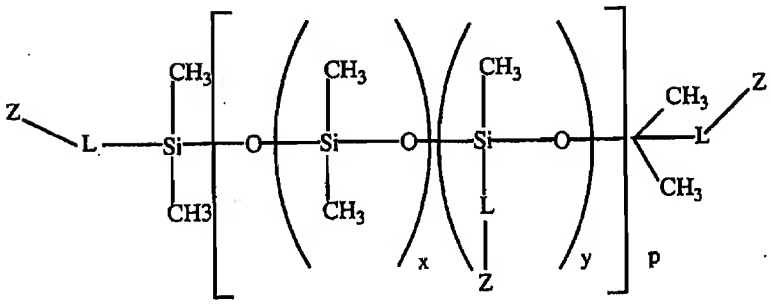
The polysiloxane copolymers of the present invention are preferably prepared as set out below.

The synthesis uses hydride terminated groups (tetramethyldisiloxane) rather than tetramethyldivinylsiloxane groups as used in Pharmacia patent US 6,066,172. This enables a far greater range of polymerisable end groups to be incorporated. For example acrylamide, methacrylate, or acrylate groups may be incorporated and these are far more reactive than the vinyl groups as outlined in US 6,066,172. The cure times are typically significantly reduced when compared to macromonomers with vinyl groups. In the present invention (meth)acryl groups are the preferred ethylenically unsaturated groups. This allows, especially with acrylamide groups, the use of significantly less cytotoxic photoinitiators. The use of tetramethyldisiloxane as the end group in synthesis of the polymer precursor offers significant advantages by using suitable precursor hydride groups most commonly used crosslinkable groups such as epoxy or isocyanate. As such the synthesis can provide cross linkable macromonomers that do not require ethylenic unsaturation to be present.





precursor



product

(II)

The R_2 groups in Formula II include –L-Z. Accordingly, the end groups of a copolymer chain may have in total two or more polymerisable groups.

R may be C_1 to C_6 or perfluronated hydrocarbon. However, a methyl group is preferred as it is the most commonly used and readily available siloxane feedstock available.

The incorporation of poly-diphenyl siloxane units into the backbone is desirable. The advantage of including these type of units is that higher refractive indices are accessible. Lower indices also result from the use of perfluorinated alkyls as R. Higher indices are an advantage because using a lens with a refractive index higher than that of the natural lens allows single vision refractive errors to be corrected in addition to presbyopia. The siloxane unit may have both a phenyl and crosslinkable group as outlined in structure (I)

The monomer unit may also have two crosslinkable groups as outlined in structure (I). The siloxane monomer unit also contains aromatic groups that include a crosslinkable group.

The preferred molecular weight range of the macromonomers is from 3000 up to 160,000 AMUs. Molecular weights above 160,000 are usually too viscous to be injectable and below 3000 too fluid to prevent spillage from the capsular bag in use. The preferred viscosity range is 1000 cP to 60,000 cP. The most preferred molecular weight range is 60,000 to 160,000 AMUs and especially 100,000 to 160,000 AMU. With reference to Formula I, the total number of monomer units t $x(n + m + o + p + q + s)$ is in the range 30 to 3000 but preferably 700 to 1500.

There are typically 100 monomer units per macromonomer chain which gives t in the range of 1 to 15, but more preferably 7 to 15 and especially 10 to 15.

The dialkyl siloxane component will generally make up by far the greatest portion of the material. In non-diphenyl containing formulations, n will be in the range of 90 – 100 and especially 98 – 100. In diphenyl based applications the value of n + o will range from 90 – 100 and especially 95 – 100.

For the alkysiloxane unit bearing the crosslinkable group, m will have a value of from 0 to 5, more preferably 0 to 2 and especially 0 to 1. Values higher

than about 2 for m are more likely to produce materials that have unacceptably high modulus for many applications.

The other crosslinkable groups specified, (p, q, s) will preferably be present such that m + p + q + s < = 2 and especially < = 1. As the value of the total increases the modulus of the polymerised material also increases.

The invention will be further described by reference to the following non limiting examples.

Example 1

This example illustrates the preparation of hydride terminated 1.2%-(poly-methylhydrosiloxane) (dimethyl siloxane) copolymer.

Preparation of stock solutions:

A stock solution of tetramethyldisiloxane was prepared by dissolving 8.00g of tetramethyldisiloxane in 353.08g of octamethylcyclotetrasiloxane.

A stock solution of 1,3,5,7-tetramethylcyclotetrasiloxane was prepared by dissolving 3.618g of 1,3,5,7-tetramethylcyclotetrasiloxane in 46.2367g of octamethylcyclotetrasiloxane.

Preparation of copolymer precursor:

5g of the tetramethyldisiloxane stock solution, 5g of the 1,3,5,7-tetramethylcyclotetrasiloxane stock solution and 40.00g of octadecylcyclotetrasiloxane were mixed in a round bottom flask under an inert atmosphere. To the mixture was added 50mL of dry toluene followed by 0.125g of trifluoromethanesulfonic acid. The reaction mixture was allowed to stir at room temperature for 3 days. 10.0g of anhydrous sodium carbonate was then added and the mixture stirred overnight, before the sodium carbonate was filtered off. The toluene solution was poured into an excess of ethanol to precipitate the siloxane copolymer which was then transferred to a kugelrohr distillation apparatus and stripped of low molecular weight species to give the poly-methylhydrosiloxane-dimethylsiloxane copolymer as a clear colourless oil (viscosity 32000 cSt, MW equivalent 72,000 AMU's, RI = 1.4048).

19.06g of the poly-methylhydrosiloxane-dimethylsiloxane copolymer prepared in Example 1 was dissolved in 107mL of dry toluene along with 3.26g of

allyl methacrylate. The reaction was initiated by the addition of 200uL of 0.02M solution of H_2PtC_{l6} in isopropanol and stirred for 4 days at room temperature. Activated carbon is added and the mixture stirred for 3 hours before the carbon was filtered off and the solution passed through a 0.2um Teflon filter. The Irgacure 819 photoinitiator (30.5mg) was then added before the solvent was removed under reduced pressure and the siloxane product heated to 40°C on a kuglelrohr apparatus under vacuum overnight to give a clear yellow oil (Viscosity 24000 cSt, MW equivalent 64,000AMU's, RI = 1.40668).

Example 2

This example illustrates the physical properties of the cured crosslinkable siloxane macromolecule in Example 1. 0.4mL of the siloxane macromolecule prepared in Example 1 was poured into a 20mm diameter polypropylene mould and pressed flat with a polypropylene top plate. The sample was irradiated with 4mW/cm-2 blue light (wavelength range 420-460nm) for 40 minutes to give a clear colourless disc. The Young's modulus of the cured polymer was measured by MFR as being 27kPa.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It will be understood that the present invention encompasses all such variations and modifications that fall within the spirit and scope.

DATED: 30 July 2002

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COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION